Responses to Major Comments on the Technical Support Document

Public Health Goal

For

Inorganic Mercury

In Drinking Water

Prepared by

Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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INTRODUCTION

The following are responses to major comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for inorganic mercury as discussed at the PHG workshop held on October 6, 1998, or as revised following the workshop. Some commenters provided comments on both the first and second drafts. For the sake of brevity, we have selected the more important or representative comments for responses. Comments appear in quotation marks where they are directly quoted from the submission; paraphrased comments are in italics.

These comments and responses are provided in the spirit of the open dialogue among scientists that is part of the process under Health and Safety Code Section 57003. For further information about

Office of Environmental Health Hazard Assessment
the PHG process or to obtain copies of PHG documents, visit the OEHHA web site at www.oehha.org.
OEHHA may also be contacted at: 301 Capitol Mall, Room 205
Sacramento, California 95814
(916) 324-7572

RESPONSES TO MAJOR COMMENTS RECEIVED

U.S. EPA, Office of Water

Comment 1: "EPA has reviewed the selected study by N.T.P. (1993), upon which OEHHA has selected to base its PHG for inorganic mercury, and concluded that besides nephropathy which was characterized by foci of tubular regeneration, thickened tubular basement membrane and scattered dilated tubules containing hyaline casts, no treatment-related effects were observed in other organs. It was noted, however, that histopathology on the other organs was not performed for any dose group except the control and high-dose rats. No BML was reported. The high mortality in the chronic study indicated that the MTD was exceeded in both dose groups and thus limits the value of the study for assessment of carcinogenic risk. It has been incorrectly justified for use to establish a PHG based on LOAEL since significant numbers of increased deaths occurred at both doses. The lower dose should not be identified as a lowest observable adverse effect level."

Response 1: It appears U.S. EPA has confused several studies noted in the NTP (1993) reference. OEHHA has only used one of the studies (subchronic rat) cited there for PHG development. The chronic (rat) study was used to support the derived PHG, not as is stated here.

Comment 2: "On October 26-27 of 1987, a panel of mercury experts met at a Peer Review Workshop on Mercury Issues in Cincinnati, OH, and reviewed outstanding issues concerning the health effects and risk assessment of inorganic mercury. The main conclusion from this panel was the fact that the most sensitive adverse effect for mercury risk assessment is formation of mercuric-mercury induced autoimmune glomerulonephritis. The productions and deposition of IgG antibodies to the glomerular basement membrane can be considered the first step in the formation of this mercuric-mercury-induced autoimmune glomerulonephritis. "

In review of the database, no one study was deemed adequate to base the RfD for inorganic mercury. Instead, three studies using the Brown Norway rat as the test strain were chosen from a larger selection of studies and based on these three studies, a DWEL of 10 ppb was recommended based on the weight of evidence from animal studies and limited human tissue data. Confidence in the DWEL is high because it was derived from an intensive review and workshop discussions of the entire inorganic mercury database and not just from one study. As EPA concluded in 1994, no revision of the MCL was needed."

Response 2: We also considered the immunotoxicological data in developing the PHG for mercury. However, it is clear that the U.S. EPA workshop panel of 1987 did not have the NTP (1993) study results to help them in their decision-making. The panel focussed on deriving water-based inorganic mercury concentrations on mechanistic studies of autoimmune glomerular nephritis. As stated in the PHG document, none of these studies met the standards of the suitability for risk assessment thus necessitating using them together. Furthermore, the panel did not take an average of the derived drinking water equivalent levels (DWELS) for each study. Rather the panel selected a value, 10 ppb. This value was chosen because the resultant MCL (after applying the Source Contribution factor of 0.1) would be 1 ppb, which they noted, was identical to the value derived by WHO. However, U.S. EPA later adopted an MCL of 2 ppb (from a source contribution factor of 0.2), thus, U.S.EPA did not completely follow the panel's recommendation. In its reevaluation in 1994, U.S.EPA chose not to change its MCL despite the 1993 NTP study; this was its own decision.

Comment 3: Consistent and accurate use of units

Units such as mg Hg/kg/day should be distinguished from mg HgCl2/kg/day accurately and consistently. On page 12 of the PHG document, doses are listed consecutively with altering units. For example, in the NTP (1993) rat study is 1.9 in mg-Hg/kg/day? If so, please correct on paragraphs 2 and 3 of this page. It is very confusing for the reader since the study was conducted to evaluate effects of HgCl2 on both rats and mice and yet, the doses are reported in "mg-Hg." EPA suggests the presentation of both doses in mg-Hg and mg-HgCl2 for greater clarity.

Response 3: OEHHA presented for each experiment, doses expressed in terms of the original mercury compound. For studies to be considered for risk assessment, the dose was first expressed in units of $HgCl_2$, followed by the dose converted to ionic mercury. Thereafter, doses were always expressed in terms of ionic mercury, particularly in the risk characterization section. OEHHA is not certain that presenting both forms of doses throughout the document will increase clarity. The proposed PHG is to regulate all species of inorganic species of mercury not merely $HgCl_2$. Furthermore, monitoring technologies in water cannot distinguish the species of mercury. Thus, the PHG must be in units of ionic mercury, and likewise, all doses supporting the mercury PHG.

Comment 4: "Dose Conversions for the NTP(1993) study should employ a 0.739 (The molecular weight ratio of 200.6 g/mole for Hg2+ ÷ 271.6 g/mole for HgCl2) factor for Hg2+ to HgCl2 and a time weighted average for 5 days/week of dosing. For example:…"

Response 4: We have rechecked all dose conversions and conclude they were done properly; the derived doses match those used by U.S. EPA and ATSDR. Again, OEHHA needs to have a PHG developed in units of mercury.

Comment 5: Interpretation of the Subchronic and Chronic NTP (1993) Results

"OEHHA selected the subchronic NTP (1993) to base its PHG value and in the process negated the results of the chronic NTP (1993) study. In the previous comment, example a. utilized a dose (1.9 mg Hg/kg/day for five days per week) that was evaluated in both subchronic and chronic studies. The subchronic study did not result in lethality, while the chronic study reported reduced survival rates in the treated male rats compared with the control. The high mortality in both treated males (1.9 and 3.7 mg-Hg/kg/day) indicates that the MTD for long term exposure was indeed exceeded in these groups.

The determination of the lowest test dose as the LOAEL is questionable due to the increased mortality rate. The tenfold uncertainty factor meant to account for the frank toxicity may not suffice. Despite this notion, the database should be evaluated as a whole and the PHG should be based on a weight-of-evidence approach, incorporating both subchronic and chronic study results."

Response 5: OEHHA used the subchronic study to base the PHG and the results of the chronic study calculation to support the PHG. Thus, a weight of evidence approach was employed. As for the concern that an additional factor of 10 for frank toxicity could not be adequately protective is not substantiated. The additional deaths in the lowest dose group were marginal, not nearly as significant as the highest dose group. The factor for frank toxicity was proposed for such situations.

University of California, Reviewer #1

Comment 1: B General Comments 1

" I would like to see all calculations used in the development of the PHG…I cannot follow the (presumed) calculations and arrive at the same LOAEL when I use the 1.9 mg/kg-day intermediate dose value provided on pages 23 and 16. I was able to arrive at the same LOAEL as used in the second set of calculations of the PHG on page 23…"

Response to Comment 1: After considering this comment, we determined that calculations involving conversions should not require much elaboration. It is understood that readers should be able to replicate standard calculations (U.S. EPA and ATSDR risk assessments follow the same policy). As to the problem of replicating the calculation of the LOAEL for the daily dose, the NTP (1993) two-year study low dose was actually 1.847 Hg mg/kg-day. This dose was expressed in the text as a rounded value. In order to retain as much precision in the calculation, the unrounded value (reflecting four significant numbers) was used in estimating the average dose over a week. Thus, there would be a minor discrepancy in the daily-adjusted dose if 1.8 Hg mg/kg-day were used instead. The text was modified to show that the unrounded value was used in the calculations.

Comment 2: General Comments 2

"The 20% to 80% default values for the relative source contribution needs to be discussed further. In fact, the 20% value is used throughout the calculations of the PHG with the assumption that this value is valid. The discussion on page 24 indicates that additional sources include ingestion of fish and ingestion/ inhalation of mercury from dental amalgam. While these sources may be significant, no attempt is made to estimate their contribution. An assessment of mercury exposure from dental amalgams was published in the journal Human and Ecological Risk Assessment (2:709-761). This exposure could be used to estimate whether the additional sources of mercury are the major contributors to mercury body burden.."

Response to Comment 2: Default values are used when more quantitative estimates of the contribution of a substance from non-water sources are not possible. The assumption of 20% contribution for mercury assumes that most of the mercury body burden is from non-water sources such as the diet and amalgams. How much mercury (particularly as inorganic mercury) contributed by these sources is not clear at this time. The referenced paper was reviewed, but in the opinion of the author, the information cannot be used to estimate body burden of inorganic mercury. The cited study does develop a total mercury body burden and estimates the contribution from amalgam. However, it implicitly assumes that all the mercury is equivalent to metallic mercury, and even develops risks based on neurotoxicity. It appears that only a fraction of metallic mercury/mercury vapor will be converted to the inorganic form, which is of primary concern for this risk assessment. Thus, the question remains as to how much inorganic mercury is contributed from food and amalgam sources.

Response to Comment 4: The 70 kg body weight assumption is based on an average adult body weight, not just of the male. It is our policy to use average adult body weights for endpoints that are not specific for female toxicity.

Comment 5 general comments

Concern is raised that variability in input parameters is not characterized and that a probabilistic framework should be used.

Response to Comment 5: It is not currently our policy to use this type of approach for development of PHGs. This type of approach requires substantially more resources and time than are available to this process.

Comment 6: Specific Comments 1.

Suggestion that other literature indicates a larger percentage of absorption of mercuric chloride than what was described in the PHG absorption section. Suggest reading Schoof and Neilson. However, that should not change the approach taken to use mercuric chloride as model form of inorganic mercury.

Response to Comment 6: The above reference is interesting, however, it only addresses absorption from soils. Absorption of small amounts of mercuric chloride from water might be different. Otherwise, there is no impact on the PHG determination.

Comment 7: Specific Comments 8

"It is stated that inorganic mercury is not volatile or permeable enough to consider the dermal or inhalation pathways for exposure. However, no information is provided to justify the statement. While I would agree that it is probably appropriate to disregard dermal and inhalation, the data used to make the assumption should be provided, e.g. permeability coefficient for the mercuric chloride."

Response to Comment 7: Our convention is to assume potential dermal and inhalation exposures for chemicals which can be classified as volatile organic compounds. Inorganic mercury is assumed to be in the ionic state in water, thus limiting its permeability through the skin. Organic and some inorganic mercury compounds are known to be more dermally permeable.

University of California, Reviewer #2

Comment 1: Data Evaluation

"The dose response assessment is appropriate. It must be noted, however, that the interpretation of the dose-response data is very conservative and that selection of a PHG of 0.0012 mg/l is most probably overly protective… In the NTP 6 month study, ….mercury was delivered by a bolus dose…. We have learned from a chronic bioassay done with chloroform bolus dose administration of an agent produces changes in a target organ….)"

Response to Comment 1:

The intent of the risk assessment for inorganic mercury is to generate a public health-protective PHG value. However, after reviewing the scientific literature, we determined that inorganic mercury is not pharmacokinetically similar to chloroform. Therefore, employing a LOAEL from a bolus study does not yield an "overly conservative" value in the same manner that has been proposed for chloroform. Chloroform, is a lipid soluble, small organic molecule assumed to have nearly total absorption. The absorption of inorganic mercury is hampered by specific uptake from the gastro-intestinal tract. The higher the concentration (as in the bolus dose) the smaller percentage of mercury is absorbed. Furthermore, the action of inorganic mercury reflects more cumulative effects with little recovery. Chloroform toxicity to the target organ appears to stem from reparative processes being overwhelmed. Thus, the interpretation that a bolus dose is always "harder" on the system is not as clear with inorganic mercury as it would be with chloroform. However, we acknowledge that there are uncertainties in the risk assessment and in attempting to address these uncertainties we have taken a health-protective approach, as is required by law.

Comment 2: Uncertainties

"Extrapolation is done throughout on a mg/kg basis. A more conservative approach (which has actually some scientific merit) would be to extrapolate on a mg/m^3 body surface area.

Response to Comment 2: This approach may or may not be more conservative for the manner in which mercury produces renal toxicity. Nevertheless, it is not currently our approach to dosimetric conversions for noncarcinogens.

Comment 3: General comments 1

" In this (and all similar) documents it would be very useful to have a table or list of abbreviations…."

Response to Comment 3: We have developed a glossary that is available on our Website, but we will consider including one for future documents.

Comment 4: General comments 2,3

Section on neurotoxicity is inadequate. More details on the possible toxicity of mercury containing amalgams.

Response to Comment 4: Neurotoxicity is a characteristic feature of elemental mercury and organic mercury exposure and not that of inorganic mercury. The PHG document for inorganic mercury focuses on the toxicity of inorganic mercury. Metallic mercury constitutes dental amalgams.

Comment 5: General comments 4

"Personally, I find the data on genetic toxicology are overemphasized. The in vitro studies are not impressive at all and of the two human studies mentioned, one was uninterpretable and the other one inconclusive. We do have data, but they are essentially meaningless for the task at hand, so why bother?"

Response to Comment 5: The genetic toxicity information may not be impressive, but it indicates that inorganic mercury is not a strong mutagen and thus adds to the weight of evidence for considering mercury as a noncarcinogen.

Comment 6: General Comment 5

"Since a consensus workshop and the WHO have come up with a value of 0.001 mg/l, why must California come up with a value of 0.0012 mg/l. This seems to be psuedoaccuracy?

Response to Comment 6: The scientific bases for the derivation of the WHO number, U.S. EPA's MCL, and OEHHA's PHG are different. They also reflect different levels of significant figures. Our PHG value is expressed in two significant figures and WHO's number is apparently one. The convention in OEHHA is to express its final value in one or two significant figures, depending on the data set and calculations.

Comment 7: Specific comments 1

"Page 1 line 2 from the bottom, "sensitive groups were identified.." but they really are not precisely identified, it just assumed that such groups exist. Is it possible to be more specific?"

Response to comment 7: In this case, they are not identified specifically, however mercury-sensitive individuals are discussed.

Comment 8: Specific comment

"Page 12, renal toxicity: increased kidney weight is throughout taken as a sign of toxicity, but this may not always hold true- at least for liver, there are circumstances where increased liver weight cannot be taken as a sign of toxicity, but as adaptation to increased metabolic demand."

Response to Comment 8: The liver adapts to toxic insult from exposure to certain substances by increasing its metabolic activity, and thus its mass. However, this does not appear to be mechanism for mercury-related renal injury. In this case, mercury is not metabolized, but deposited into/or directly reacts with (assuming the immunologic reaction) the glomerulus. Such activity is not readily reversible and is a cumulative change. Therefore, it is likely that a change in kidney weight upon mercury intoxication is an adverse effect.

Comment 9: Specific Comments

"Page 14, last paragraph in Developmental: is it acceptable to rely on information that has only been

an old textbook of pathology gives the lowest fatal dose in man as 0.18 g - considerably less than the 0.5 mentioned here."

Response to Comment 10: Our literature review did not include this information. Without a specific citation, we cannot include this information.

Comment 11: Specific comments

"Page 18: I was pleased to see that "pink disease" acrodynia is being discussed. Isn't the underlying mechanism of immunological nature? And if so, would this provide some clues to sensitive subgroups?"

Response to Comment 11: Acrodynia is a specific sensitivity to mercury, and might explain why certain individuals cannot tolerate amalgam fillings. OEHHA concludes that with the degree of uncertainty factors used in the risk assessment, sensitive individuals will be protected.

Comment 12: Specific Comments

"page 21, second para "Carcinogenic effects:" Would the Fitzhugh and Schroeder studies be considered to be adequate according to current-day criteria for a carcinogenesis study and thus must they be mentioned?"

Response to Comment 12: These studies do meet those criteria, and they do evaluate mercuric chloride specifically. The Schroeder study in particular is a lifetime study and thus adds an additional dimension not found in current day study protocols.

Comment 13: Specific comments

"Page 21, last 3 lines" *Questioned the comment from the NTP report, which questions the significance of the appearance of carcinomas without the appearance of adenomas and hyperplasia.*

Response to Comment13: In order to relate the incidence of carcinomas with exposure to mercuric chloride, the appearance of carcinomas should have been preceded by that of adenomas and hyperplasia in a dose-related manner. At lower doses, hyperplasia should have been at least noted, but it was not. Thus, the appearance of carcinomas may not be related to dosing as judged by NTP.

Comment 14: Specific Comments

"Page 22, line 4 form top: what is the IARC classification?

Response to Comment 14: Group 3, and this is included in the revised document.

Comment 15: Specific Comments

"Page 23: the added uncertainty factor of 10 for "frank toxicity" is really not explained and hard to understand."

Response to Comment 15: The factor for frank toxicity is now expressed as a "modifying factor" and is explained in the Risk Characterization section of the technical support document.

Comment 16: "Page 23: first line" *It was not clear whether administration of mercuric chloride in the NTP study was by gavage or by drinking water.*

Response to Comment 16: It is by gavage and this point was clarified in the document.

Comment 17: Specific Comments

" Hg concentrations are sometimes given as mg/l, ug/l or ppb or ppm."

Response to Comment 17: At present, both ppm (ppb) and mg/L (µg/L) units are used by federal and state agencies interchangeably. We have attempted to use only one unit within a discussion so as to reduce confusion.

Comment 18: Specific Comments

"Page 25, line 18 form top: why would a committee decision not be as good as a more precise

Response to Comment 18: Please also see response to Comment 6.

Legislation requires PHGs be derived using the best science and risk assessment methodology. Estimates for safe values derived by the consensus workshop and the WHO were based on information available at that time (now at least 12 years old). They had to apply less rigorous standards for risk assessment (i.e., inadequate studies were used followed by speculation) in order to derive their values. Although useful for comparison, the WHO committee's conclusions were not based on as comprehensive of an analysis as our PHG risk assessment.